Comments of Gina M. Solomon, M.D., M.P.H. (on behalf of the Natural Resources Defense Council), Barbara Brenner (on behalf of Breast Cancer Action), Jeanne Rizzo (on behalf of the Breast Cancer Fund), Bob Gould, M.D. (on behalf of San Francisco Bay Area Physicians for Social Responsibility) and Jonathan Parfrey (on behalf of Los Angeles Physicians for Social Responsibility)

Introductory Remarks

The Natural Resources Defense Council, The Breast Cancer Fund, San Francisco Bay Area Physicians for Social Responsibility, Los Angeles Physicians for Social Responsibility and Breast Cancer Action appreciate the opportunity to comment on the OEHHA draft health effects assessment for environmental tobacco smoke (ETS). Our organizations are all actively involved in efforts to prevent significant environmental threats to public health.

Comment 1:

The listing of ETS as a Toxic Air Contaminant (TAC) under Health and Safety Code sections 39650-39674 is a scientific "no brainer." There is a veritable mountain of scientific data showing that ETS is a significant health hazard, and is causally associated with cancer, cardiac disease, asthma, other respiratory disease, and developmental problems in children including Sudden Infant Death Syndrome (SIDS). It is absolutely clear that this chemical mixture qualifies for listing as a TAC. ETS contains numerous chemicals that are already listed as TACs, such as benzene, 1,3-butadiene, various polycyclic aromatic hydrocarbons (PAHs), acrylamide, ammonia, hexavalent chromium, formaldehyde, and lead. Another somewhat similar complex mixture, diesel exhaust, was listed as a TAC several years ago. Based on its list of ingredients, ETS could essentially be summarized as diesel exhaust with added nicotine and tobacco-specific nitrosamines (TSNAs). Therefore we strongly endorse the conclusions of the draft document and support the proposed listing of ETS as a TAC.

The draft health effects assessment is an agonizingly detailed review of the enormous scientific literature on ETS. Although the quality of the science is high, and we believe that the document accurately reflects the literature, we are deeply concerned that this review sets a standard that is ultimately detrimental to public health. Spending the decade of research and the thousands of person-hours required to create a document that is this lengthy and detailed for a TAC listing determination inevitably means that very few chemicals or mixtures will move through the listing process. As California implements increasingly severe budget cuts, it is likely that OEHHA will suffer from worsening staff shortages. If every document is expected to be a multi-volume review comparable to this draft, we will see very little activity toward listings of environmental hazards.

A prior document listing ETS as a toxic air contaminant was fully endorsed by the Scientific Review Panel in June of 1997. This document was begun in June of 2001 and was in process for two and a half years, during which time the California Air Resources Board did not have the

authority to regulate ETS as a toxic air contaminant. Meanwhile, as we can see from this draft, we can reliably state that while this document was being written about three thousand children were born in California with low birthweight due to ETS exposures, three hundred infant deaths from SIDS occurred, hundreds of thousands of people suffered otherwise potentially preventable asthma exacerbations, and thousands of deaths from myocardial ischemia occurred due to exposures to ETS. Some number of these illnesses might have been prevented had ARB been granted the regulatory authority sooner to take aggressive action against ETS. It is therefore necessary for OEHHA to balance scientific thoroughness with its mandate to implement the laws designed to protect public health.

We firmly believe that it is possible to produce a high quality scientific review that is a fraction of the length of this document, and that could be completed in a small fraction of the time. There is nothing in the law or the science that requires OEHHA to produce a definitive encyclopedia on the effects of every chemical that it reviews. It is only the fear (and reality) of industry litigation, and the creeping precedent of ever-larger reports that drive OEHHA to such extremes in document preparation. Shorter review documents would save the time and effort of the agency scientists, and of the reviewers charged with reading the documents. Shorter documents can be just as accurate scientifically and can be much more useful for protecting public health, since five such documents could potentially be produced in the time spent on one document such as the one reviewed today.

Due to the extreme length of the document, we focused our review on the introductory material and the discussion of ETS and breast cancer. Although there are likely other important and interesting issues throughout the rest of the draft, we were simply unable to give these chapters the review they deserved in the time available.

Response:

OEHHA thanks the commentators for their remarks. While OEHHA is perhaps uniquely conscious of the volume of information and level of detail in the arguments presented in the document, we are unable to agree that a shorter document for this complex chemical mixture would address the legislative mandate that this process is designed to serve. Additionally, OEHHA was gratified to see that the similarly extensive document prepared in 1997 was seen as a useful contribution to the scientific debate on some of the (then) contentious issues relating to health effects of ETS exposure. It is hoped that the present update will similarly contribute to this ongoing debate, which requires careful and detailed consideration of the evidence, particularly where this extends or modifies the conclusions of the earlier document.

Comment 2:

Petition to Bring ETS before the DART Identification Committee

Although we did not focus our current review on Chapters 3-5 of the document, we could not help noticing that there is now even more extensive evidence demonstrating that ETS is a reproductive and developmental toxicant. In the interest of 'reducing, reusing, and recycling' this document, and in the hope of further protecting the public from this extremely hazardous exposure, we therefore petition OEHHA to take ETS out of the normal glacial prioritization process and to present these three chapters to the Developmental and Reproductive Toxicant Identification Committee at its next meeting for reconsideration of the listing of ETS under Proposition 65 [California Health and Safety Code 25249.5 et *seq]*

Response:

OEHHA have referred this request to the group responsible for Proposition 65 implementation. We are completing the process of public and peer review under AB 1807 before bringing the document to the DART Identification Committee in order to properly focus on the response to comments and revisions as appropriate to the document.

Comments on Chapter 1

Comment 3:

The definition of ETS is somewhat inconsistent with the discussion on page 1-4 and 1-5 about ETS exposure in animal studies. The latter discussion appears to state that only 'sidestream smoke' is relevant to ETS exposure, whereas the definition on page 1-2 makes clear that ETS is actually comprised of 'mainstream smoke' that escapes when the smoker inhales, exhaled mainstream smoke, and sidestream smoke. Thus the animal tests that carefully expose animals only to sidestream smoke do not appear to reflect the full range of realistic exposures to ETS. It is incorrect to say that "A few recent studies have used exposures characterized as 'sidestream smoke,' which is considered more relevant to the assessment of the effects of ETS exposure." In fact, a mixture of mainstream and sidestream smoke would be most relevant. Although this point is a minor one, it bears correcting to avoid the appearance of dismissing animal data that do not include only sidestream smoke. In reality, virtually all of the animal experiments could be classified as exposures to ETS at various doses.

Response:

OEHHA agrees in part with this comment. Our discussion on page 1-3 of what is sidestream smoke is correct. On page 1-6, the last sentence refers back to the previous sentence. We believe that sidestream smoke exposure in animal studies is important and more germaine to ETS than animal studies of only mainstream smoke, primarily because sidestream smoke is about

90% or more of ETS (U.S.EPA, 1992). The comment that a mixture of sidestream and mainstream smoke is the most relevant is correct. We have added a phrase to the last sentence and an additional sentence to clarify our meaning. The last two sentences of the paragraph now read "A few recent studies have used exposures characterized as "sidestream smoke", which is considered more relevant to the assessment of the effects of ETS than studies of only mainstream smoke. Of course a mixture of exhaled mainstream and sidestream smoke would be most relevant."

Comment 4:

The discussion of measures of effect and weight of evidence evaluations on pages 1-5 through 1-7 is very useful. It does make sense to evaluate the quality of the studies and the sources and likely direction of any bias when evaluating the weight of evidence. It is also important not to dismiss studies that failed to achieve statistical significance at the 0.05 level, since such studies may indeed be affected by factors such as insufficient power or by extensive nondifferential misclassification of exposure. We also agree that inconsistencies in scientific results are almost inevitable in any body of research, and that the finding of results that are not consistent from one study to another should not be a reason to automatically dismiss the results or to give up and declare that 'the jury is still out' on an issue. Instead, it makes sense to try to determine if there may be explanations for the inconsistencies and to see if it is still possible to draw conclusions based on the entirety of the available evidence. It is helpful for OEHHA to explain these important issues in the introductory material to avoid confusion about how the draft was prepared, and to help members of the public understand these important scientific issues. We believe that this discussion reflects a thoughtful approach to the literature review that is well-justified scientifically.

Response:

Thanks for the comment. We hope that the reader understands we have considered the totality of the evidence, including information from carcinogenicity studies of ETS constituents (for example), and not just individual epidemiological studies .

Comments on Chapter 7 Section on Breast Cancer

Comment 5:

We applaud OEHHA for the groundbreaking review of the links between ETS and breast cancer on pages 7-91 to 7-155, and we agree with the conclusions reached. There has been a lot of important research over the past few years into this important issue, and the weight of evidence points strongly toward a causal association. The large majority of the epidemiologic studies found elevated odds ratios, although not all were statistically significant. The studies with the

best efforts at exposure assessment found greater odds ratios and were more likely to achieve statistical significance, in keeping with the prediction that nondifferential misclassification of exposure status tends to bias toward the null. The literature on active smoking and breast cancer supports the unifying hypothesis that tobacco smoke is an important breast cancer initiator, but is also anti-estrogenic and therefore has an anti-promoter effect. Therefore the timing of the exposure becomes extremely important. Among smokers, exposure when the breast is still particularly vulnerable to carcinogens before pregnancy and lactation, appears to be clearly associated with breast cancer development, whereas exposure after pregnancy and lactation and in the postmenopausal period has the opposite effect, especially in overweight women who would normally have higher levels of circulating endogenous estrogens after menopause.

Response:

OEHHA is appreciates these comments, which are in line with our overall conclusions on the association between ETS exposure and breast cancer.

Comment 6:

It is clear that tobacco smoke contains numerous chemicals that cause mammary tumors in laboratory animals. In addition to the fifteen chemicals listed in Table 7.4D, the following seven chemicals should also be added: acrylamide, isoprene, N-nitrosodiethylamine [1], propylene oxide, cadmium [2], nitromethane [3], and nitrobenzene [4].

Response:

OEHHA thanks the commentators for this additional information, and has modified Table 7.4D to reflect the occurrence and carcinogenic effects of these additional compounds. All the proposed additions were included, with the exception of cadmium, which, as noted in the footnote to the comment, is rather anomalous in that mammary tumors appeared in male rats only. (The critical study in fact included only male rats, but the result was not replicated in other somewhat similar studies in either sex.) Also the statistical significance of the result is fairly weak, and probably because of these features neither IARC in their most recent review (IARC Monographs, volume 58, 1993) nor NTP's 10th Annual Report on Carcinogens (ROC) chose to put emphasis on this result. All the other new entries have been validated by reference

[1] 9th Report on Carcinogens. US Department of Health and Human Services, Public Health Service, National Toxicology Program, 2000.
[2] IRIS http://www.epa.gov/iris/search.htm. Note that cadmium causes mammary tumors in male rats only.
[3] ToxNet (CCRIS-Chemical Carcinogenesis Research Information System): http://www.nlm.nih.gov/pubs/factsheets/ccrisfs.html
[4] Gold LS, Neela B. Manley, Thomas H. Slone, Jerrold M. Ward. Compendium of Chemical Carcinogens by Target Organ: Results of Chronic Bioassays in Rats, Mice, Hamsters, Dogs, and Monkeys Toxicologic Pathology 29: 639-652 (2001).

to the ROC or IARC. Additionally, the table was updated with new information on smoke composition, including values for the additional compounds, obtained from the newly published IARC monograph (Volume 83, 2004) on Tobacco Smoke and Involuntary Smoking. The revised table is shown below.

Table 7.4D Chemicals identified in tobacco smoke which induce mammary tumors.

Compound	Cigarette main-stream smoke (amount per cigarette) [a]	Cigarette side-stream smoke (amount per cigarette) [b]	Cigarette smoke-polluted environments [c]	Cigar (C) or Pipe (P) smoke (µg/100 g) [d]	IARC Classific-ation	Mammary gland tumors: Affected Species [e]
Aromatic hydrocarbons						
Benzene	28 - 106 µg	71 - 134 µg	5 - 22 µg/m^3	P: 34400 C: 9200-24600	1	Mouse
Benzo[a]pyrene	5.6 - 41.5 ng	52 - 95 ng	0 - 3.6 ng/m^3	C: 1.8-5.1 P: 8.4	2A	Rat
Dibenz[a,h]anthracene	4 ng	[f]			2A	Mouse [g]
Dibenzo[a,e]pyrene	Present				2B	Rat[h]
Dibenzo[a,h]pyrene	Present				2B	Rat[h]
Dibenzo[a,i]pyrene	1.7 - 3.2 ng				2B	Rat[h]
Dibenzo[a,l]pyrene	Present				2B	Rat[h]
Nitrosamines						
N-nitrosodiethylamine	0 - 25 ng		Up to 8.6 ng/m^3		2A	Rat
N-Nitrosodi-*n*-butylamine	0 - 3.0				2B	Mouse
Aliphatic compounds						
Acrylamide	Present				2A	Rat
Acrylonitrile	8 - 39 µg	24 - 44 µg			2B	Rat
1,3-Butadiene	24 - 123 µg	81 - 135 µg	19 µg/m^3		2A	Mouse, rat
Isoprene	288 - 1193 µg	743 - 1163 µg	83 - 150 µg/m^3	C: 24500-63300	2B	Rat
Nitromethane	0.5 - 0.6 µg				2B	Rat[i]
Propylene oxide	0 - 100 ng				2B	Rat[j]
Urethane	20 - 38 ng				2B	Mouse, hamster
Vinyl chloride	11 - 15 ng			C: 0.14-0.27	1	Rat, mouse, hamster
Arylamines and nitroarenes						
4-Aminobiphenyl	2 - 8 ng	21 – 32 ng			1	Rats
Nitrobenzene	25 µg				2B	Mice[k]
ortho-Toluidine	30 - 200 ng				2A	Rats

Footnotes:

[a] IARC Monographs volume 83 (2004) Tobacco Smoke, citing preferentially Table 1.10 (the 1999 Massachusetts Benchmark Study), or else Table 1.14.

[b] IARC Monographs volume 83 (2004) Involuntary Smoking, citing Table 1.3 (the 1999 Massachusetts Benchmark Study)

[c] IARC Monographs volume 83 (2004) Involuntary Smoking, citing mainly Jenkins et al., 2000

[d] IARC Monographs volume 38, Tobacco smoking and IARC Monographs volume 83 (2004) Tobacco Smoke.

[e] NTP: 10th Annual Report on Carcinogens (2002) unless otherwise indicated

[f] Blank cell = no data available

[g] IARC Monographs, Volume 3 (1973).

[h] Cavalieri et al. (1989; 1991).

[i] IARC Monographs, Volume 77 (2000).

[j] IARC Monographs, Volume 60 (1994).

[k] IARC Monographs, Volume 65 (1996).

Comment 7:

The findings of PAH-DNA adducts in humans exposed to environmental sources of polycyclic aromatic hydrocarbons, including cigarette smoke (ie. the Whyatt et al. study cited on page 7-136 and the Rundle et al. study described on page 7-91) are a helpful part of the causal chain. The fact that the PAH-DNA adducts do not appear to be a biomarker that is highly specific to cigarette smoke is not surprising, given the other environmental and dietary sources of this pollutant. Yet the finding of these adducts in human tissues, particularly in breast cancer tissues, does add to the overall weight of evidence, since we know that cigarette smoke is one important source of PAH exposure.

Response:

OEHHA agrees that the developing body of literature relating biomarkers of exposure to eventual outcomes is important and has continued to support the causal chain of evidence. Studies in humans now include evidence that levels of PAH-DNA adducts in normal breast tissue are related to tobacco smoke exposure and that levels of those adducts are associated with the likelihood of developing breast cancer. We have added several newer studies on these to the discussion in the revised document.

Comment 8:

There are a couple of inconsistencies between Table 7.4E on page 7-141 and the text that follows. In particular, the table classifies the Hirayama 1984 study and the Jee 1999 study as 'unlikely' to have missed important exposures to ETS. Yet in the subsequent tables these same studies are classified as 'likely' to have missed important ETS exposures. Because both studies looked only at the husband's smoking history, it seems at first glance that they should be classified as likely to have missed important exposures. However, since both studies were done in Korea during a time when perhaps it may have been unusual for women to work outside the home, occupational exposures may have been unlikely and such a history unnecessary. Still, it seems that the complete neglect of ETS exposures during childhood would merit classification of both studies in the 'likely' to have missed important exposures category, unless cigarette smoking was very unusual in Korea in the 1930's-1950's. At any rate, these studies should be classified consistently as either likely or unlikely to have missed important ETS exposures.

Response:

The text regarding these studies has been clarified. Hirayama and Jee are now listed in tables 7.4E and subsequently as likely to have missed important exposures. As you point out, the degree to which this may be true may be far less than studies from other regions due to cultural factors.

In the summary statistics that follow table 7.4E they were already listed as likely to have missed important exposures and therefore no change in those numbers will be necessary.

Comment 9:

In this draft document, OEHHA calculates estimates of ETS-related morbidity and mortality due to a list of diseases, including California-specific figures for childhood asthma induction and exacerbation, bronchitis or pneumonia in children, lung cancer, SIDS, low birth weight, and otitis media. Yet for some reason, OEHHA fails to calculate estimates of ETS-related morbidity and mortality due to breast cancer. Such an omission makes no sense. OEHHA concludes correctly that the data support a causal association between ETS exposure and breast cancer. OEHHA is also able to calculate a summary statistic of the overall magnitude of the risk (a relative risk of 1.92 when all important ETS sources are collected). The overall population burden of breast cancer in California is well known. Therefore it would be straightforward to calculate the attributable fraction of breast cancer due to ETS. We searched the draft in vain for such a calculation and finally concluded that the calculation was omitted. It is critically important for the public to know the proportion of breast cancer occurrence in California that would potentially be eliminated if exposure to ETS were prevented. Breast cancer is unfortunately all too common, and any public health intervention that may decrease the burden of this disease in California is of utmost importance. Therefore we strongly urge OEHHA to add a calculation of the attributable risk for breast cancer and ETS to the final version of this document.

Response:

We recognize the significance of our finding that ETS is a causative factor in breast cancer, and would like to see preventive measures taken as a result of our findings (not just for breast cancer but all the other endpoints associated with ETS). However, it is quite difficult to estimate attributable risk with any certainty given the number of known risk factors for breast cancer that contribute to the high rate of this disease including age at menarche, age at menopause, age at first birth, parity, and whether the woman breast fed her babies. Although perhaps a relatively crude attributable risk could be developed, we felt it was best to avoid the calculation until we have a better way to account for these other known risk factors.